Solvolysis of Di-2-pyridylketone Methiodide

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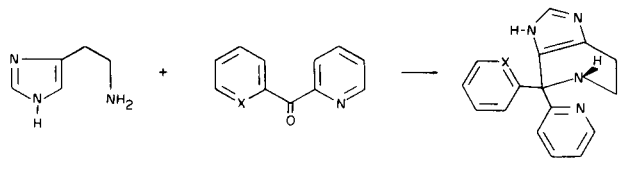
Di-2-pyridylketone methiodide undergoes a facile nucleophilic substitution reaction with various alcohols followed by subsequent cleavage and elmination of pyridinium methiodide and the correspoing picolinates.

J. Heterocyclic Chem., **19**, 1549 (1982).

We have recently initiated a study of the synthesis and biological evaluation of a series of diaryl-4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridines (1). The condensation of histamine with di-2-pyridylketone **1** to give structure **2** is a typical example within this series (Scheme 1).

Scheme 1

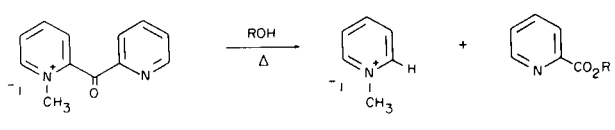


1, X = N **2**, X = N
3, X = N^+-CH_3 **4**, X = N^+-CH_3

Compound **2** was found to exhibit some rather interesing biolgoical activity and, in an effort to further characterize this system, we attempted a similar condensation of histamine and the corresponding di-2-pyridylketone methiodide, **3**. To our surprise, this reaction did not give rise to the expected methylated tetrahydroimidazopyridine **4**, but instead, solvolysis of the ketone occurred to give pyridinium methiodide as the major product. This observation led us to begin a study of the relative chemical reactivity of this methylated ketone with various alcohols.

When the parent dipyridylketone **1** is refluxed in either 1-butanol or ethanol there is no apparent suggestion of nucleophilic cleavage of the dipyridyl system and only unreacted starting material is recovered. However, when the ketone is methylated with methyl iodide in acetone (2) and then allowed to react with ethanol under reflux conditions, there is a rapid solvolysis and subsequent cleavage of the diaryl system to give pyridinium methiodide in 74% and the associated ethyl picolinate, (Scheme 2). A similar solvolysis can be observed with both methanol and 1-butanol to give the methyl and butyl esters respectively. A

Scheme 2



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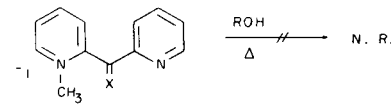
R = Et, Me, n-Butyl

similar ring cleavage reaction of di-2-pyridylketone **1** has been described by Mather and Sauermilch (4) which required strong alkali and elevated temperatures to give rise to pyridine and picolinic acid.

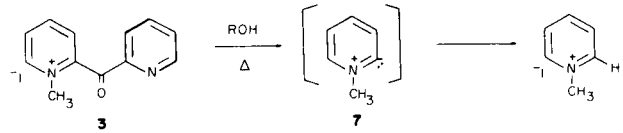
The enhanced electrophilicity of the methylated ketone **3** is undoubtedly due in part to the strong activating influence of the pyridinium moiety. It is interesting to note, however, that neither the oxime **5** nor the thiosemicarbazone analog **6** undergo cleavage under solvolytic conditions (Scheme 3), (2), (3).

Scheme 3

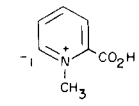


5, X = N-OH
6, X = N-N-C-N-H_2 (H, S)

We are currently investigating this facile solvolytic cleavage in hopes of demonstrating the possible involvement of the intermediate **7** in the reaction mechanism. The same intermediate has been proposed by Howe and Ratts (5) in a study of the thermal dicarboxylation of homarine hydrochloride **8**, and a similar structure was described by Abramovitch in a study of the base-catalyzed deprotonation of certain substituted pyridinium salts (6).



3 **7**



8

EXPERIMENTAL

Melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus. The ir spectra were recorded on a

Perkin-Elmer 137 Spectrometer. The nmr spectra were recorded on a Varian T-60 Spectrometer; the chemical shifts are reported on the δ scale relative to tetramethylsilane. Microanalyses were performed by the M-H-W laboratories, Pheonix, Arizona.

Di-2-pyridylketone Methiodide **3**.

This compound was prepared using the method of Ginsburg (7). A 0.5 g sample of the parent ketone **1** was dissolved in 50 ml of acetone and treated with a 5 molar excess of methyl iodide. Upon standing the salt **3** precipitated out of solution to give 0.6 g (64%) of a yellow, crystalline solid. The methylated ketone was recrystallized from ethanol/ether, mp 197°; ir (potassium bromide): 3100, and 1700 cm^{-1}; nmr (deuterated dimethylsulfoxide): δ 4.3 (s, 3H, NCH_3), 6.3 (m, 1H, C-5), 6.8 (m, 3H, C-3, C-3′, C-5), 7.2 (m, C-4, C-4′, C-6′), 7.8 (d, 1H, C-6) ppm.

Anal. Calcd. for $C_{12}H_{11}IN_2O$: C, 44.17; H, 3.37; N, 8.58. Found: C, 44.19; H, 2.98; N, 8.53.

Solvolysis of **3** with Ethanol.

A solution of 0.2 g of **3** in 20 ml of absolute ethanol was refluxed for 24 hours. The clear solution was concentrated *in vacuo* and then titrated with ether to give 0.1 g (74%) of crystalline pyridinium methiodide, mp 110°; ir (potassium bromide): 3200 and 1650 cm^{-1}; nmr (deuterium oxide): δ 4.8 (s, 3H, NCH_3), 8.5 (m, 2H, C-3, C-5), 8.9 (m, 1H, C-4), 9.3 (d, 2H, C-2, C-6) ppm.

Anal. Calcd. for C_6H_8IN: C, 32.59; H, 3.62; N, 6.33. Found: C, 32.76; H, 3.87; N, 6.39.

The filtrate from the above reaction was concentrated further to give 0.7 g (76%) of a pale yellow oil whose infrared spectrum was identical with that of ethyl picolinate (8).

Solvolysis of **3** with Methanol.

When a solution of 0.2 g of **3** in 20 ml of absolute methanol was refluxed overnight and treated following the procedure described above, a 55% yield of pyridinium methiodide could be obtained together with a 70% yield of the methyl ester. The methylpicolinate was identified by comparative infrared analysis with an authentic example of the ester.

Solvolysis of **3** with 1-Butanol.

A solution of 0.2 g of **3** in 20 ml of 1-butanol was refluxed for 24 hours and subsequently diluted with ether to give 0.12 g (71%) of pyridinium methiodide. The resulting filtrate was concentrated *in vacuo* to give 0.1 g (89%) of a yellow oil whose infrared spectrum was identical with that of butyl picolinate.

Acknowledgment.

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REFERENCES AND NOTES

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